Review Paper

Role of Angiotensin II in the Evolution of Diastolic Heart Failure

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More than half of all persons with heart failure (HF) have diastolic HF. The prevalence of diastolic HF increases from 46% in persons younger than 45 years to 59% in those 85 years and older. The annual mortality rate associated with diastolic HF is >10%. Diagnosis is based on signs and symptoms of HF, elevated plasma B-type natriuretic peptide, preserved left ventricular systolic function, and evidence of diastolic dysfunction by Doppler examination on two-dimensional echocardiography. Approximately 80% of patients with diastolic HF have increased left ventricular mass and a history of hypertension. Neurohormonal activation is a key aspect of this condition. Studies suggest that activation of the renin-angiotensin-aldosterone system, specifically direct cardiac effects of angiotensin II and aldosterone, contributes to the pathogenesis and progression of diastolic dysfunction. Hence, there is a rationale for use of agents that antagonize the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists, in patients with heart failure. (J Clin Hypertens. 2005:7:740–747) ©2005 Le Jacq Ltd.

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Heart failure (HF) is a hemodynamic and neurohormonal syndrome that is becoming increasingly prevalent as the population ages and as new medical and surgical therapies reduce cardiovascular mortality.[1] HF is commonly divided pathophysiologically into systolic and diastolic HF, because each has an independent etiology, prevalence, prognosis, and treatment.[2,3] Although the signs and symptoms of diastolic and systolic HF are often the same (e.g., dyspnea on exertion, orthopnea, fatigue, and edema), the epidemiology, determinants, and gross anatomic pathophysiology are quite different.

Common risk factors for the development of diastolic HF include hypertension, age, diabetes mellitus, chronic kidney disease, and coronary artery disease.[4] Abnormalities in the diastolic effects of the left ventricle lead to hemodynamic derangements.[5] It is believed that these hemodynamic abnormalities precede the development of symptoms and may be triggered by early and possibly long-standing neurohormonal activation. In patients with diastolic HF, left ventricular (LV) active relaxation is impaired, end-diastolic and left atrial pressures are elevated, and end-diastolic volume is reduced. Moreover, the severity of diastolic dysfunction independently predicts development of atrial fibrillation.[6] In turn, atrial fibrillation results in the loss of arterial contraction ("atrial kick"), which further worsens congestive symptoms and may accelerate the progression of diastolic dysfunction to overt HF. These underlying pathogenic factors lead to increased LV stiffness, a fundamental characteristic of HF (Figure 1).[7,8]

It has been easier to characterize systolic HF than diastolic HF, the definitions of which range from various degrees of abnormal LV filling patterns to more recently proposed catheterization-derived LV

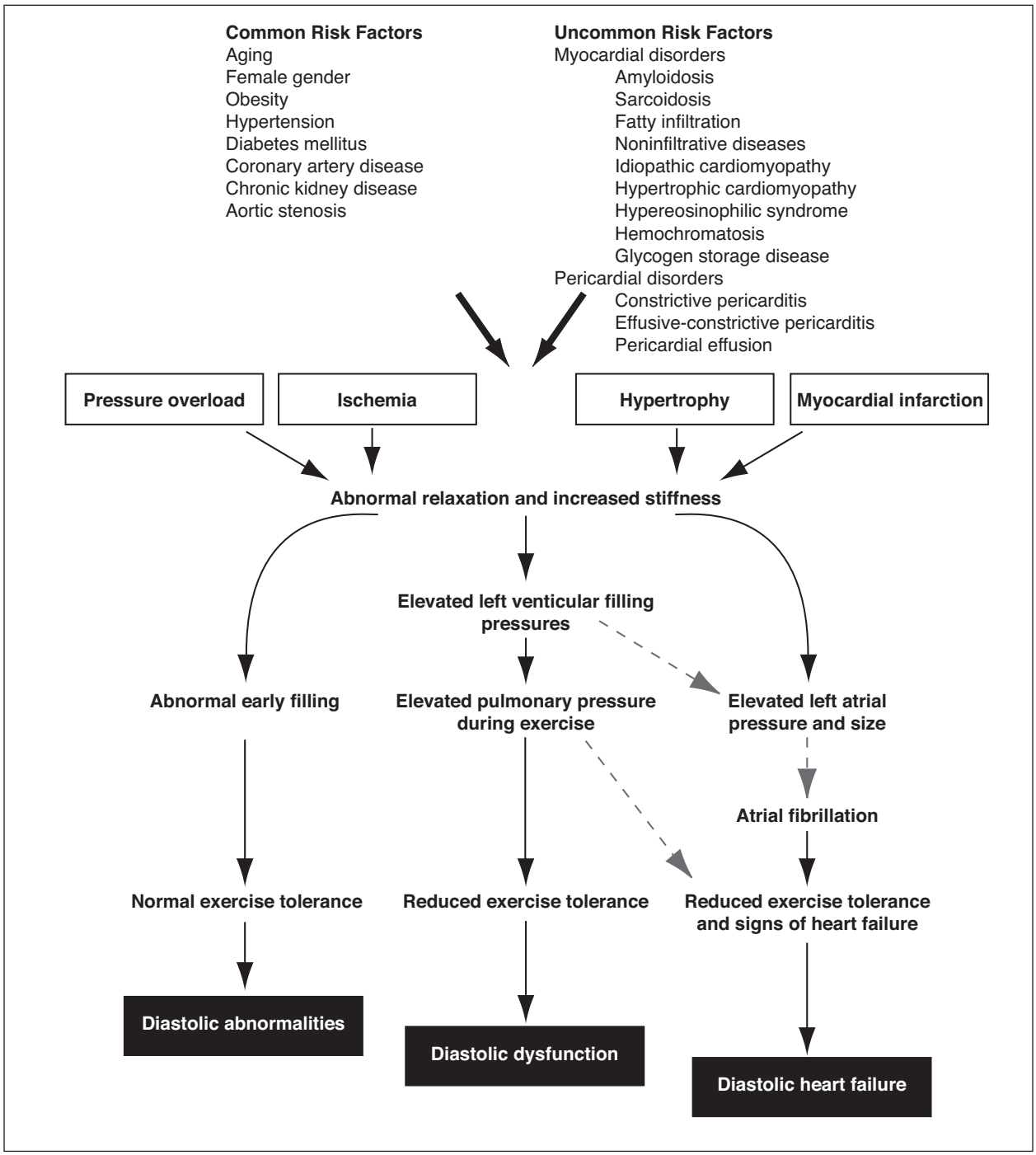

Figure 1. Risk factors, predisposing conditions, and hemodynamic determinants of diastolic heart failure. Adapted from Cardiovasc Res. *2000;45:813–825.*[7]

relaxation, filling, or distensibility indices.[9–11] A simple ejection fraction cut-point of 45% is a practical surrogate marker of diastolic HF and has been used in large epidemiologic studies.[9] However, the gold standard diagnostic technique for diastolic HF is Doppler echocardiographic demonstration of diastolic dysfunction in a patient with the HF syndrome and preserved ejection fraction.[11,12] Doppler mitral inflow and pulmonary venous flow velocity-derived variables are widely used to evaluate diastolic dysfunction. These indices, however, are influenced by many physiologic factors, especially alterations in filling pressures. The results therefore can be inconclusive. Newer modalities, such as Doppler tissue imaging and color M-mode, are less affected by loading conditions of the heart.[13]

Detailed echocardiographic evaluation can accurately grade the severity of diastolic dysfunction.[13]

Table. Characteristics of the REACH Echocardiography/Electrocardiography Cohort: Prevalence of Diastolic Heart Failure (Ejection Fraction ≥45%) by Subgroup in a Cohort of Persons With Heart Failure

Characteristic	Prevalence (%)
Age (yr)	
<45	46
45–64	47
65–84	56
≥85	59
Gender	
Male	42
Female	59
Race	
White	43
Black	54

REACH=Resource Utilization Among Congestive Heart Failure; p=0.001 for trend. Derived from *Congest Heart Fail.* 2005;11:6–11.[15]

Echocardiography is invaluable in assessing the presence and grading of diastolic dysfunction in patients with early signs of the condition, such as exertional dyspnea. However, routine echocardiographic monitoring of diastolic function is not currently recommended in hypertensive patients without evidence of HF.

EPIDEMIOLOGY: THE REACH STUDY

The largest population study of diastolic HF to date is the Resource Utilization Among Congestive Heart Failure (REACH) study.[14] The study followed 3471 subjects (mean age 66±15 years) for an average of 32.4±30.1 months after baseline echocardiography.[14,15] Based on Framingham criteria for HF in addition to an ejection fraction cutoff of ≥45%, 1811 patients (52%) were determined to have diastolic HF, and the relative incidence of diastolic dysfunction increased with age (Table).[15,16] This prevalence was similar to rates in other recent reports.[17–22] Importantly, there were 958 deaths (58%) among patients with systolic HF and 850 deaths (47%) among patients with diastolic HF during the course of the study. The annualized age-, sex-, and race-adjusted mortality rates for the first 72 months were 11.2% for diastolic HF and 13.0% for systolic HF (p=0.001).[15] Of note, longer QRS duration was associated with higher mortality among subjects with diastolic and systolic HF (p=0.05 and p=0.01, respectively), suggesting that intrinsic myocardial disease affects the conduction system in both HF subtypes.[15] In addition, the principal REACH study demonstrated that the prevalence of HF worsened throughout the 1990s.[14]

RATIONALE FOR RAAS BLOCKADE IN DIASTOLIC HF

Results of therapeutic trials conducted in hypertensive patients with conditions that are commonly associated with diastolic HF provide important treatment guidance. Specifically, findings in patients with neurohormonal activation, LV hypertrophy, and renal dysfunction provide a strong rationale for reducing renin-angiotensin-aldosterone system (RAAS) activity with an angiotensin receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor in patients with diastolic HF.

Neurohormonal Activation

Underlying the symptoms of HF is a balancing act among the actions of the RAAS and other regulatory systems (sympathetic nervous, endothelin, and arginine-vasopressin systems), as well as counter-regulatory hormones such as brain natriuretic peptide (BNP).[5] The RAAS has varied roles in the regulation of cardiac function, including early receptor-mediated effects such as second messenger generation and delayed responses such as protein synthesis and cell growth.[23] Activation of these neurohormonal systems leads to an increase in central and systemic fluid volume. As pulmonary capillary wedge pressure rises, and systemic mechanoreceptors detect arterial underfilling, there is a homeostatic response leading to further activation of the sympathetic nervous system and the RAAS, and to nonosmotic release of arginine vasopressin (Figure 2).[24]

Angiotensin (Ang) II directly affects the myocardium by increasing LV wall tension to compensate for reduced contractility.[8,25–27] Ang II directly modulates cardiac function by its effects on myocardial metabolism and hypertrophic growth.[28] This hypertrophy is reversed by ACE inhibition.[25–27] Similarly, treatment with ARBs has been shown to improve LV filling in patients with impaired diastolic function but without LV hypertrophy.[29] Further, Ang II has indirect cardiac effects mediated by the central nervous system, which include stimulation of thirst and sympathetic outflow, stimulation of aldosterone synthesis and release, decreased renal excretion of sodium, and maintenance of vascular tone.[30]

Ang II and aldosterone appear to have synergistic effects on adverse LV remodeling; hence, both are treatment targets in patients with HF. Ang II is an important stimulus for the adrenal glands to release the mineralocorticoid aldosterone. Aldosterone reduces renal excretion of water and sodium,

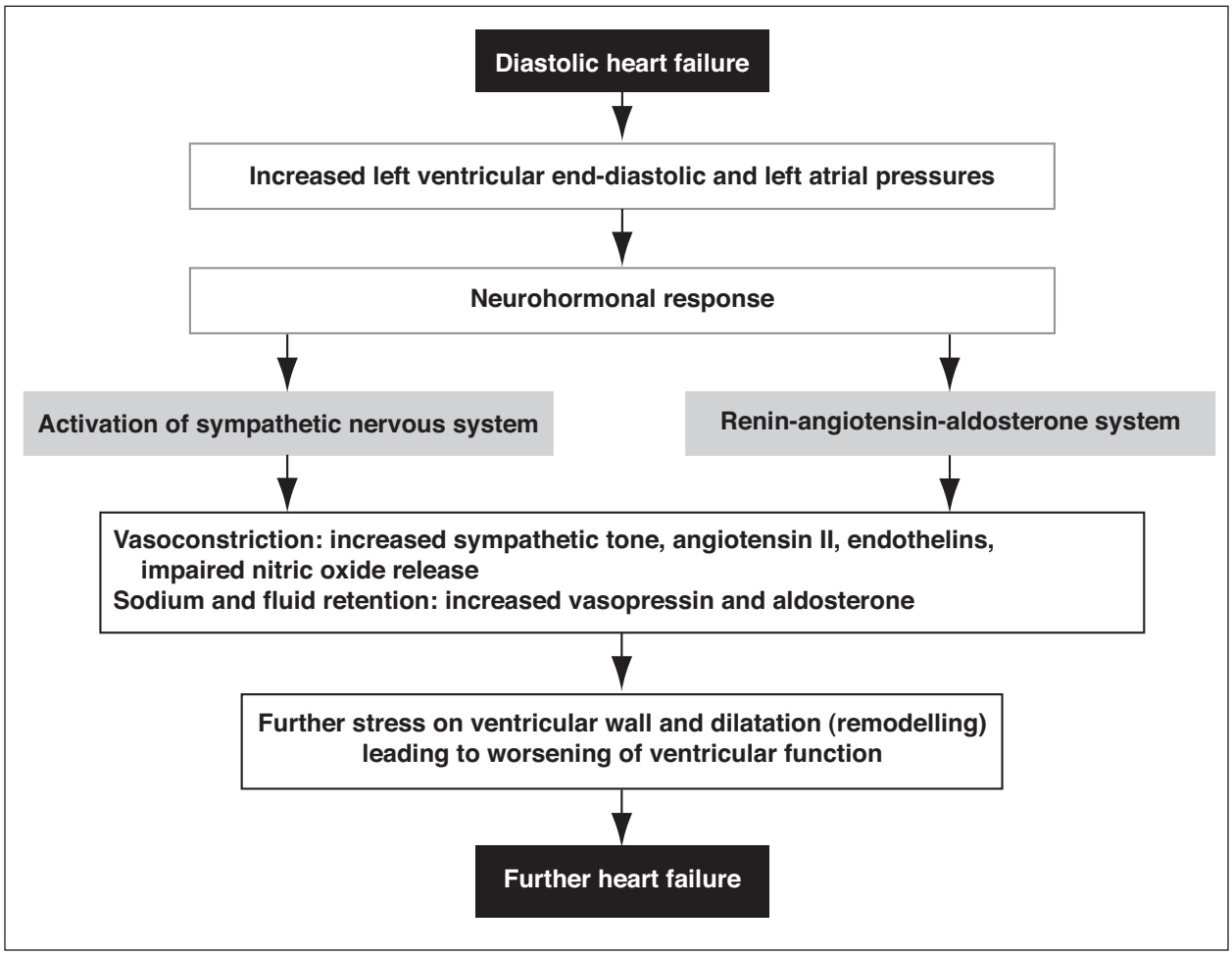

Figure 2. Neurohormonal activation in diastolic heart failure

thereby elevating blood pressure. Aldosterone may play a direct role in the myocardium via mineralocorticoid receptors, which modulate the extracellular matrix and promote collagen deposition.[31] Aldosterone receptor blockade with spironolactone has been reported to inhibit collagen synthesis and thereby reduce cardiac fibrosis.[32] Aldosterone antagonism also improves endothelial function, promotes sodium excretion, and lowers systemic vascular resistance.[33] Aldosterone concentrations are also acutely affected by ACE inhibitor and ARB treatment; however, this effect may not persist even though data from the Valsartan Heart Failure Trial (Val-HeFT), which studied patients with systolic HF, show that the ARB valsartan reduced aldosterone throughout the trial (up to 24 months).[34–36]

Elevations in BNP can be quite helpful in confirming the diagnosis of HF, although its utility in distinguishing systolic dysfunction from diastolic dysfunction is limited.[37] N-terminal pro-BNP (a precursor of BNP) was reduced by treatment with the ARB losartan but was increased by treatment with the β blocker atenolol in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.[38] Similarly, results from Val-HeFT showed significant, sustained reduction in BNP with valsartan ($p<0.0001$).[39]

Fibrosis and LV Hypertrophy

Decreased early diastolic filling, which is characteristic of diastolic dysfunction due to LV chamber stiffness, generally correlates with increased LV mass. Indeed, nearly 80% of patients with diastolic HF have increased LV mass and a history of hypertension.[40] In human subjects with a genetic risk for developing hypertension, however, diastolic dysfunction may precede the development of LV hypertrophy, presumably due to structural changes in the myocardium such as altered collagen and myocardial architecture.[41] Possible mechanisms for diastolic dysfunction in the absence of LV hypertrophy include changes in intrinsic myocardial stiffness, myocardial fibrosis with interstitial collagen deposition, and altered chamber geometry.[42]

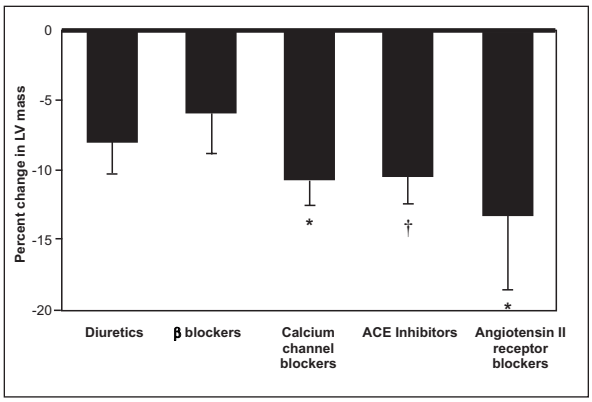

*Figure 3. Reduction in left ventricular (LV) mass index (as percentage from baseline) with antihypertensive treatment by drug class. Mean values and 95% confidence intervals adjusted for change in diastolic blood pressure and treatment duration are shown. ACE=angiotensin-converting enzyme; *p<0.05 vs. β blockers; †p<0.01 vs. β blockers (after Bonferroni correction). Adapted from* Am J Med. *2003;115:41–46.*[53]

Other etiologies for LV hypertrophy include hypertrophic cardiomyopathy and valvular lesions (e.g., aortic stenosis), which cause chronic LV pressure overload and induce a compensatory increase in LV mass.[7] In coronary artery disease, diastolic dysfunction is the earliest sign of ongoing ischemia. After myocardial infarction, changes in cardiac structure include replacement fibrosis, hypertrophy of the residual myocardium, changes in the collagen network, myocyte reorganization, stimulation of the neurohormonal system, cytokine activation, and altered gene expression, all of which may lead to increased myocardial stiffness.[7]

In vivo studies have implicated Ang II in the cardiac hypertrophy associated with hypertension.[42] The effects of Ang II on LV tissue include deposition of intercellular matrix (collagen, fibrin) and an increase in intracellular calcium.[43–45] Recent studies have implicated Ang II in the stimulation of myocardial collagen synthesis and regulation of collagen degradation by attenuation of interstitial matrix metalloproteinase activity.[44,46,47] An animal model of the transition from hypertension to compensatory LV hypertrophy to impaired relaxation to diastolic HF shows that ACE messenger RNA is upregulated and Ang II type 1 receptor messenger RNA is not downregulated.[48] Studies in rat models of genetic hypertension demonstrate that blockade of Ang II type 1 receptors enhances collagen degradation and reversal of myocardial fibrosis.[45] Inhibition of the RAAS prevents or reverses this increase in fibrillar collagen but may not consistently reduce myocardial stiffness.

The clinical characteristics of patients with diastolic HF (e.g., history of hypertension or myocardial infarction and increased LV mass) may be comparable to those of subjects in the Heart Outcomes Prevention Evaluation (HOPE) study, who had normal systolic function.[40,49] Baseline histories of cardiovascular events were similar between HOPE patients and those enrolled in the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved Trial, who had preserved LV function.[49,50] The HOPE trial demonstrated significantly lower rates of death, myocardial infarction, and stroke in patients receiving ACE inhibitor-based treatment compared with those not receiving an ACE inhibitor. HOPE also demonstrated a reduction of LV hypertrophy and prevention of the development of HF, independent of morning office blood pressure readings.[49,51] However, a small ambulatory blood pressure substudy suggests that blood pressure reduction with an ACE inhibitor was greater than in the non-ACE inhibitor group, especially at night. This may explain some of the benefit seen with ACE inhibitor therapy.[52] Thus, reduction of LV hypertrophy or prevention of progression of LV hypertrophy is an important therapeutic goal in patients with diastolic HF.

Indeed, most studies have shown the greatest regression of LV hypertrophy occurred with ARBs and ACE inhibitors compared with β blockers and calcium channel blockers (Figure 3).[53] In Val-HeFT,[54] valsartan significantly reduced LV internal diastolic diameter ($p<0.00001$) compared with standard HF therapy. This result extended the findings of an earlier study that showed a greater degree of regression of LV mass index with valsartan compared with the calcium channel blocker amlodipine in patients with severe LV hypertrophy.[55] Moreover, in the LIFE trial,[56] Cornell voltage-duration and Sokolow-Lyon voltage measurements of LV hypertrophy were reduced to a greater extent by losartan than by atenolol ($p<0.001$).

Renal Disease

Renal insufficiency, a common cardiovascular comorbidity in persons with diastolic dysfunction, is an independent prognostic factor in patients with diastolic and systolic dysfunction ($p=0.002$).[57] Renal insufficiency is associated with several changes in vascular pathophysiology that may further worsen cardiovascular outcomes, including disruptions in the endothelial nitric oxide balance and hyperactivation of the sympathetic nervous system and the RAAS.[58]

A meta-analysis found that the antiproteinuric effects of ACE inhibitor-based treatment were superior to other therapies (primarily β blockers

or calcium channel blockers).[59] In patients with chronic renal failure, ACE inhibitor-based treatment has also been associated with regression of LV mass and improvement in LV diastolic function.[60] In addition, major ARB trials focusing on subjects with diabetes have also demonstrated reductions in microalbuminuria, overt proteinuria, and progression to end-stage renal disease.[61–64] Of note, a large majority of subjects receiving RAAS blockade in these studies also received diuretic therapy.

NEED FOR CLINICAL TRIALS IN DIASTOLIC HF

Since diastolic HF was recognized relatively late in our understanding of HF, there is a paucity of completed randomized treatment trials that specifically address this population. The first large, prospective, randomized, double-blind, placebo-controlled trial designed to include patients specifically with diastolic HF was the CHARM-Preserved Trial;[50] however, this investigation did not require Doppler evidence of diastolic dysfunction and had no BNP entry criteria.[65] Hence, there is concern that this study may have included patients who did not have diastolic HF at all.[65] Still, the approximately 3000 subjects had supporting signs or symptoms of HF, an LV ejection fraction of >40%, and a history of hospital admission for HF (69%).[50]

In addition to standard background therapy, which usually included a diuretic, subjects received either the ARB candesartan (titrated to a maximum dose of 32 mg/d) or matching placebo.[50] The primary outcome (time until first hospitalization for HF or cardiovascular death) did not reach statistical significance, although the trend favored ARB treatment (adjusted hazard ratio, 0.86; p=0.051). The secondary end point of hospitalization for HF was significantly lower with ARB therapy (p=0.017).[50] One may postulate that since the epidemiology and pathophysiology of diastolic HF differ from systolic HF, the most effective dose or timing of administration of the ARB may also differ and may have been suboptimal in this trial. Even so, CHARM-Preserved suggests the possibility that ARBs may prove useful in patients with diastolic HF. It is clear that more studies of basic approaches using RAAS inhibitors in populations with verified diastolic HF are needed.

CLINICAL IMPLICATIONS

As in systolic HF, a principal goal in diastolic HF is to reduce the impact of the RAAS with either ACE inhibitors or ARBs and, possibly, aldosterone antagonists. In addition, since the sympathetic nervous system is potentially a primary trigger for activation of the RAAS in diastolic HF, there is a strong rationale for the use of β blockers in these patients.

Blood pressure control and, consequently, relative control of left-sided filling pressures is necessary. Multiple agents, which should include a RAAS-blocking agent and usually a diuretic, are often required. Pharmacotherapy is primarily based on reducing disease progression by providing effective blood pressure control and, via the regression of LV hypertrophy, reversing adverse cardiac remodeling, neurohormonal and sympathetic nervous system activation, and renal dysfunction. Although volume control with judicious use of diuretics is important, it is potentially difficult to achieve. Underdiuresis leads to chronic volume overload and contributes to continued adverse LV remodeling, while overdiuresis, given the tight pressure-volume relationship that exists in diastolic HF, can lead to hypotension. Heart rate control is considered the next priority, so agents that prolong diastolic filling time are desirable since they allow for more complete filling of the left ventricle and improve relative forward flow. β Blockers, calcium channel blockers, and digitalis have all been used in this role without prospective trial evidence in diastolic HF. In cases of atrial fibrillation with poorly controlled heart rate, atrioventricular node ablation with insertion of a permanent pacemaker can be a possible strategy to provide rate control.

CONCLUSIONS

Diastolic HF is the most common form of HF, and it is particularly prevalent among elderly women and in hypertensive individuals. Although the prognosis for diastolic HF is slightly better than that for systolic HF, the annual mortality rate is >10%. Despite the prevalence and risk associated with this condition, few trials provide treatment guidance. Even so, there is sound rationale for blockade of neurohormonal activation in diastolic HF as well as for therapies that treat common comorbidities. The RAAS is associated with neurohormonal activation and a range of pathologic conditions in diastolic HF, including LV remodeling and renal dysfunction. For this reason, ARBs and ACE inhibitors appear to be well suited to treat diastolic HF and associated comorbidities. Future studies involving well-defined cohorts of subjects with verified diastolic HF are needed to test this theory and clarify the clinical utility of these treatments.

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